SEASONAL INFLUENZA

✓DISEASE AND EPIDEMIOLOGY

Clinical Description

Influenza is an acute respiratory disease characterized by abrupt onset of fever and respiratory symptoms such as cough (usually nonproductive), sore throat, and coryza, as well as systemic symptoms such as headache, muscle aches, and fatigue. Acute symptoms typically last 2–7 days, although malaise and cough may continue for 2 weeks or longer.

Complications of influenza virus infection include secondary bacterial pneumonia and exacerbation of chronic health conditions. Primary influenza viral pneumonia is an uncommon complication with a high fatality rate. Complications occurring in children can include otitis media, febrile seizures, encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye syndrome. Reye syndrome is a complication that occurs almost exclusively in children taking aspirin, primarily in association with influenza B (or varicella zoster), and presents with severe vomiting and confusion, which may progress to coma due to swelling of the brain.

Causative Agent

Influenza is caused by RNA viruses from the *Orthomyxoviridae* family. There are three types of influenza viruses: A, B, and C. Influenza A viruses are further categorized by their H (hemagglutinin) and N (neurominidase) membrane glycoproteins.

Differential Diagnosis

Viruses that cause symptoms similar to influenza include: respiratory syncytial virus (RSV), adenovirus, parainfluenza virus, and human metapneumovirus virus.

Laboratory Identification

Laboratory diagnosis of influenza is recommended when the prevalence of influenza disease is low (which is usually at the beginning or end of the influenza season), when a patient is severely ill with influenza-like symptoms, and when other diseases that may cause influenza-like illness are known to be circulating in the community.

Culture

Virus isolation is a crucial component of virologic surveillance, as only culture isolates can provide specific information regarding circulating strains and subtypes of influenza viruses. However, culture is also time consuming and may not be appropriate when trying to determine treatment and prophylaxis. Appropriate clinical specimens include nasal washes, nasopharyngeal aspirates, nasal and throat swabs, tracheal aspirates, and bronchoalveolar lavages. Specimens should be taken within 72 hours of onset of illness.

RT-PCR

RT-PCR is the most sensitive method for influenza virus detection and the gold standard for influenza diagnosis. Since the 2009 H1N1 pandemic, RT-PCR has become more widely available. Many RT-PCR tests are now capable of subtyping influenza A viruses. Additional information on RT-PCR diagnosis is available from the CDC.

DFA
DFA testing detects the influenza virus directly from clinical samples. It is a rapid test with fairly good sensitivity and specificity. However, it can't subtype influenza A viruses.

Serology
Serologic confirmation of influenza requires demonstration of a significant rise in influenza IgG. The acute-phase specimen should be taken less than 5 days from onset, and a convalescent specimen taken 10–21 days (preferably 21 days) following onset. Serological testing results for human influenza on a single serum specimen is not interpretable and is not recommended. Serologic testing is not generally recommended, except for research and public health investigations.

Rapid Influenza Diagnostic Tests (RIDTs)
Rapid diagnostic testing for influenza antigen permits those in office and clinic settings to assess the need for antiviral use in a timelier manner. These rapid tests differ in the types of influenza viruses they can detect and whether they can distinguish between influenza types. Results of these rapid influenza antigen detection tests can be available in 15 minutes or less. When interpreting results of a rapid influenza test, physicians should consider the positive and negative predictive values of the test in the context of the level of influenza activity in their community. Additional information on the use of RIDTs for influenza diagnosis is available from the CDC.

Utah Public Health Laboratory (UPHL) Testing
UPHL tests for influenza virus by RT-PCR and viral culture. For testing at the Utah Public Health Laboratory, samples should be submitted within 72 hours of collection.

Treatment
Two FDA-approved influenza antiviral medications are recommended for use in the United States: oseltamivir (Tamiflu®) and zanamivir (Relenza®).

Table of Antiviral Medications Recommended for Treatment of Influenza

Antiviral Agent	Active Against	FDA Approved For	Not Recommended for Use In
Oseltamivir (Tamiflu®)	Influenza A and B	2 weeks and older	NA
Zanamivir (Relenza®)		7 years and older	People with underlying respiratory disease

Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who

- is hospitalized;
- has severe, complicated, or progressive illness; or
- is at higher risk for influenza complications.

Persons at higher risk for influenza complications recommended for antiviral treatment include:

- children aged younger than 2 years;
- adults aged 65 years and older;
- persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);
- persons with immunosuppression, including that caused by medications or by HIV infection;
- women who are pregnant or postpartum (within 2 weeks after delivery);
- persons aged younger than 19 years who are receiving long-term aspirin therapy;
- American Indians/Alaska Natives;
- persons who are morbidly obese (i.e., body-mass index is equal to or greater than 40); and
- residents of nursing homes and other chronic-care facilities.

When indicated, antiviral treatment should be started as soon as possible after illness onset, ideally within 48 hours of symptom onset. However, antiviral treatment might still be beneficial in patients with severe, complicated or progressive illness and in hospitalized patients when started after 48 hours of illness onset, as indicated by observational studies. Additional information on treatment recommendations can be found on the CDC website: Antiviral Drug Recommendations.

Aspirin should not be used for infants, children, or teenagers because they may be at risk for contracting Reye syndrome following an influenza infection.

Antivirals require pre-authorization under Medicaid in ordinary circumstances. At each elevation of the influenza activity level, UDOH will consider requesting that Medicaid suspend this requirement.

Case Fatality

The number of influenza-associated deaths varies substantially by year, influenza virus type and subtype, and age group. Death is reported in 0.5–1 per 1,000 cases. The majority of deaths (<90%) occur among persons 65 years of age and older.

Reservoir

Humans are the only known reservoir of influenza types B and C. Influenza A may infect humans, birds (predominantly poultry) and mammals (such as swine).

Transmission

Influenza is primarily transmitted via large droplets generated when infected persons cough or sneeze. Transmission may also occur through direct contact or indirect contact with respiratory secretions such as when touching surfaces contaminated with influenza virus and then touching the eyes, nose or mouth. The virus has good persistence in the environment. Attack rates range from 10-20% in the general population, but can be as high as 50% in closed populations such as nursing homes.

Susceptibility

All humans are thought to be susceptible to influenza, although certain high-risk populations are more likely to suffer from severe illness or death. People at high risk for developing flu-related complications include:

- Children younger than 5, but especially children younger than 2 years of age
- Adults 65 years of age and older
- Pregnant women
- American Indians and Alaskan Natives
- People with certain medical conditions, including:
    - Asthma
    - Neurological and neurodevelopmental conditions [including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury].
    - Chronic lung disease (such as chronic obstructive pulmonary disease [COPD] and cystic fibrosis)
    - Heart disease (such as congenital heart disease, congestive heart failure and coronary artery disease)
    - Blood disorders (such as sickle cell disease)
    - Endocrine disorders (such as diabetes mellitus)
    - Kidney disorders
    - Liver disorders
    - Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
    - Weakened immune system due to disease or medication (such as people with HIV or AIDS, or cancer, or those on chronic steroids)
    - People younger than 19 years of age who are receiving long-term aspirin therapy
    - People who are morbidly obese (Body Mass Index, or BMI, of 40 or greater)

Because of the variability of the virus, infection does not produce immunity.

Incubation Period

The influenza virus has a short incubation period, typically 1-3 days.

Period of Communicability

In adults, influenza is transmissible from 1 day before symptom onset until 5 days after onset. Children can transmit the virus 10 or more days after symptom onset. Immunocompromised persons can shed virus for weeks to months after infection.

Infected persons are assumed to be shedding virus and potentially infectious from the day prior to illness onset until resolution of fever. Because resolution of fever is difficult to measure when people utilize antipyretics, infected persons should be assumed to be contagious up to 7 days after illness onset. Some persons who are infected might shed virus and be contagious for longer periods (i.e., young infants, immunosuppressed, and immunocompromised persons).

Epidemiology

Influenza viruses undergo gradual, continuous change in the hemagglutinin and neurominadase proteins, known as antigenic drift. As a result of these antigenic changes, antibodies produced

to influenza viruses as a result of infection or vaccination with earlier strains may not be protective against viruses circulating in later years.

Antigenic shift, which occurs only in influenza A viruses, is a major change in one or both surface antigens (H or N) that occurs at varying intervals. Antigenic shifts are probably due to genetic recombination (an exchange of a gene segment) between influenza A viruses, usually those that affect humans and birds. An antigenic shift may result in a worldwide pandemic if the virus is efficiently transmitted from person to person.

✓PUBLIC HEALTH CONTROL MEASURES

Public Health Responsibility

Influenza surveillance in the United States consists of five categories of information collected from eight data sources.

Viral Surveillance

- U.S. WHO collaborating laboratories
- National Respiratory and Enteric Virus Surveillance System (NREVSS)
- Novel influenza A reporting

Outpatient Illness Surveillance

- U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet)

Mortality Surveillance

- 122 Cities Mortality Reporting System
- Influenza-associated pediatric mortality reporting

Hospitalization Surveillance

- Influenza Hospitalization Network (FluSurv-NET)

Summary of the Geographic Spread of Influenza

- State and territorial epidemiologists' reports of influenza activity level

Prevention

The primary method to prevent influenza infection is yearly vaccination. “Respiratory etiquette” is another way to prevent infection, and includes:

- Staying away from people who are sick and staying away from other people when you are sick. Don’t go to work, school, church, or other places where people gather if you are sick.
- Covering your mouth and nose when you cough or sneeze. Use a disposable tissue and throw it away when you are done.
- Washing your hands with soap and warm water, or use alcohol-based hand sanitizers frequently.
- Avoid touching your eyes, nose, or mouth. Germs spread this way.
- Try to avoid close contact (i.e., within 6 feet) with sick people.
- If you get sick with influenza symptoms, CDC recommends that you stay home from work or school and limit contact with others to keep from infecting them.

Chemoprophylaxis

Oseltamivir and zanamivir can be used for chemoprophylaxis of influenza. CDC does not recommend widespread or routine use of antiviral medications for chemoprophylaxis so as to limit the possibilities that antiviral resistant viruses could emerge. Antiviral chemoprophylaxis generally is not recommended if more than 48 hours have elapsed since the last exposure to an infectious person.

Table of Antiviral Medications Recommended for Chemoprophylaxis of Influenza

Antiviral Agent	Active Against	FDA Approved For	Not Recommended for Use In
Oseltamivir (Tamiflu®)	Influenza A and B	1 year and older	NA
Zanamivir (Relenza®)		5 years and older	People with underlying respiratory disease

Situations where antiviral chemoprophylaxis should be considered include:

- Prevention of influenza in persons at high risk of influenza complications during the first two weeks following vaccination after exposure to an infectious person.
- Prevention for people with severe immune deficiencies or others who might not respond to influenza vaccination, such as persons receiving immunosuppressive medications, after exposure to an infectious person.
- Prevention for people at high risk for complications from influenza who cannot receive influenza vaccine due to a contraindication after exposure to an infectious person.
- Prevention of influenza among residents of institutions, such as long-term care facilities, during influenza outbreaks in the institution. For more information, see IDSA guidelines website.

Vaccination

CDC's Advisory Committee on Immunization Practices (ACIP), a panel made up of medical and public health experts, recommends that everyone aged 6 months and older receive an annual influenza vaccination. Annual vaccination is necessary to account for differences in circulating strains.

Types of Influenza Vaccine Available in the United States

Vaccine Type	Approved for	Administered via
Inactivated influenza vaccine (IIV)	Anyone 6 months of age or older, regardless of the presence of chronic illness	Intramuscular route
Live attenuated influenza vaccine (LAIV)	Healthy, non-pregnant persons aged 2-49 years	Intranasal route
Recombinant HA influenza vaccine (RIV)	Persons aged 18-49 years	Intramuscular route

Trivalent influenza vaccines contain three different vaccine viral antigens, one each from an influenza A(H1N1) virus, an influenza A(H3N2) virus, and an influenza B virus. Quadrivalent influenza vaccines contain the same three antigens as trivalent vaccines, along with an antigen from a second influenza B vaccine virus strain.

Isolation and Quarantine

Voluntary Isolation

Symptomatic patients should not attend work or school if they are sick, and should stay away from public places to avoid further transmission. Persons who become ill with influenza symptoms should stay at home for 7 days after onset of symptoms, or for 24 hours after symptoms resolve, whichever is longer.

Health Care Facilities

Infection control recommendations can be found in CDC's Influenza Infection Control in Health Care Facilities.

Quarantine: N/A

✓REPORTING

Influenza-associated hospitalizations are a reportable disease in Utah. Influenza-associated pediatric mortality is a reportable disease, both nationally and in Utah.

Reporting Tables

Table of criteria to determine whether an influenza-associated hospitalization should be reported to public health authorities.

Criterion	Reporting
Clinical Evidence	
Admission date 14 days or less *after* a positive influenza test	O
Admission date 3 days or less *before* a positive influenza test	O
Laboratory Evidence	
Positive influenza diagnostic test	N

Note:
N = This criterion in conjunction with all other "N" and any "O" criteria in the same column is required to report or confirm a case.
O = At least one of these "O" criteria in each category (i.e., clinical evidence and laboratory evidence)—in conjunction with all other "N" criteria in the same column—is required to report or confirm a case.

Table of criteria to determine whether an influenza-associated pediatric mortality should be reported to public health authorities.

Criterion	Reporting
Clinical Presentation	
Death of a person <18 years of age	N
Illness clinically compatible with influenza infection	N
Cause of death not related to influenza	A
Recovery from febrile, respiratory illness prior to illness leading to death	A
Laboratory Findings	
Identification of influenza A or B virus infections by at least one of the following:	N
Influenza virus isolation from respiratory specimens	O

Reverse-transcriptase polymerase chain reaction (RT-PCR) from respiratory specimens positive for influenza virus	O
Immunofluorescent antibody staining (direct or indirect) of respiratory specimens positive for influenza virus	O
Positive rapid influenza diagnostic testing of respiratory specimens	O
Positive immunohistochemical (IHC) staining for influenza viral antigens in respiratory tract tissue from autopsy specimens	O
Four-fold rise in influenza hemagglutination inhibition (HI) antibody titer in paired acute and convalescent sera	O

Notes:
S = This criterion alone is sufficient to report
N = This criterion in conjunction with all other "N" and any "O" criteria in the same column is required to report or confirm a case. A number following an "N" indicates that this criterion is only required for a specific clinical presentation
O = At least one of these "O" criteria in each category (i.e., clinical presentation and laboratory findings)—in conjunction with all other "N" criteria in the same column—is required to report or confirm a case. A number following an "O" indicates that this criterion is only required for a specific clinical presentation.
A = This criterion is indicated as an exclusion criteria. Do not report cases that meet this criterion.

Influenza-Associated Hospitalizations (2012)
Case Definition

Clinical Criteria

- Hospital admission* date 14 days or less after a positive influenza test, OR
- Hospital admission* date 3 days or less before a positive influenza test

Laboratory Criteria for Diagnosis

Evidence of a positive influenza test by at least one of the following methods:

- Positive viral culture for influenza
- Positive immunofluorescence antibody staining (Direct [DFA] or indirect [IFA]) for influenza
- Reverse transcriptase polymerase chain reaction (RT-PCR) positive for influenza
- Serologic testing positive for influenza
- A positive, unspecified influenza test noted in the medical chart (e.g., a written note in the admission H&P or discharge summary)
- A positive commercially available rapid diagnostic test for influenza

Case Classification

Confirmed

A case that meets the clinical and laboratory evidence criteria.
*Patients who are admitted for hospitalization and discharged the same day are considered to have been hospitalized as long as their visit involved an admission, not just an ER or outpatient visit.

Classification Table

Criteria for defining a case of influenza-associated hospitalization.

Criterion	Confirmed
Clinical Evidence	
Admission date 14 days or less *after* a positive influenza test	O
Admission date 3 days or less *before* a positive influenza test	O
Laboratory Evidence	
Positive viral culture for influenza	O
Positive immunofluorescence antibody staining (Direct [DFA] or indirect [IFA]) for influenza	O
Reverse transcriptase polymerase chain reaction (RT-PCR) positive for influenza	O
A positive, unspecified influenza test noted in the medical chart (i.e., a written note in the admission H&P or discharge summary)	O
A positive commercially available rapid diagnostic test for influenza	O

Note:
O = At least one of these "O" (Optional) criteria in each category (e.g., clinical evidence and laboratory evidence) in the same column—in conjunction with all "N" criteria in the same column—is required to classify a case.

Influenza-Associated Pediatric Mortality (2004)

Case Definition

An influenza-associated death is defined for surveillance purposes as a death resulting from a clinically compatible illness* that was confirmed to be influenza by an appropriate laboratory or rapid diagnostic test. There should be no period of complete recovery between the illness and death. Influenza-associated deaths in all persons <18 years of age should be reported.

A death should not be reported if:

- There is no laboratory confirmation of influenza virus infection;
- The influenza illness is followed by full recovery to baseline health status prior to death;
- The death occurs in a person 18 years or older;
- After review and consultation there is an alternative agreed upon cause of death.

Laboratory Criteria

Laboratory testing for influenza virus infection may be done on pre- or post-mortem clinical specimens, and include identification of influenza A or B virus infections by a positive result by at least one of the following:

- Influenza virus isolation in tissue cell culture from respiratory specimens;
- Reverse-transcriptase polymerase chain reaction (RT-PCR) testing of respiratory specimens;
- Immunofluorescent antibody staining (direct or indirect) of respiratory specimens;
- Rapid influenza diagnostic testing of respiratory specimens;
- Immunohistochemical (IHC) staining for influenza viral antigens in respiratory tract tissue from autopsy specimens;
- Four-fold rise in influenza hemagglutination inhibition (HI) antibody titer in paired acute and convalescent sera.

Case Classification

Confirmed

A death meeting the clinical case definition that is laboratory confirmed. Laboratory or rapid diagnostic test confirmation is required as part of the case definition; therefore, all reported deaths will be classified as confirmed.

*****A clinically compatible illness is defined as fever >100° Fahrenheit with cough or sore throat.

Comment

Serologic testing for influenza is available in a limited number of laboratories, and should only be considered as evidence of recent infection if a four-fold rise in influenza (HI) antibody titer is demonstrated in paired sera. Single serum samples are not interpretable.

Classification Table

Criteria for defining a case of influenza-associated pediatric mortality.

Criterion	Confirmed
Clinical Presentation	
Death of a person <18 years of age	N
Illness clinically compatible with influenza infection	N
Cause of death not related to influenza	A
Recovery from febrile, respiratory illness prior to illness leading to death	A
Laboratory Findings	
Identification of influenza A or B virus infections by at least one of the following:	N
Influenza virus isolation from respiratory specimens	O
Reverse-transcriptase polymerase chain reaction (RT-PCR) from respiratory specimens positive for influenza virus	O
Immunofluorescent antibody staining (direct or indirect) of respiratory specimens positive for influenza virus	O
Positive rapid influenza diagnostic testing of respiratory specimens	O
Positive immunohistochemical (IHC) staining for influenza viral antigens in respiratory tract tissue from autopsy specimens	O
Four-fold rise in influenza hemagglutination inhibition (HI) antibody titer in paired acute and convalescent sera	O

Notes:
S = This criterion alone is sufficient to report
N = This criterion in conjunction with all other “N” and any “O” criteria in the same column is required to report or confirm a case. A number following an “N” indicates that this criterion is only required for a specific clinical presentation
O = At least one of these “O” criteria in each category (i.e., clinical presentation and laboratory findings)—in conjunction with all other “N” criteria in the same column—is required to report or confirm a case. A number following an “O” indicates that this criterion is only required for a specific clinical presentation.
A = This criterion is indicated as an exclusion criteria. Do not report cases that meet this criterion.

✓CASE INVESTIGATION

Case Investigation Process

Influenza-Associated Hospitalizations

Influenza testing is recommended for hospitalized patients with suspected influenza. Public health in Utah strongly encourages hospitalized patients with symptoms compatible with influenza, who test negative by RIDT, have confirmatory testing performed by RT-PCR. UPHL can provide confirmation, and can use the residual eluate on a nasopharyngeal swab that is left over from certain rapid influenza tests. Empiric antiviral treatment should be initiated as soon as possible without the need to wait for any influenza testing results. Initiation of antiviral treatment as early as possible is recommended for hospitalized patients. While antiviral treatment should ideally begin within 48 hours of symptom onset, data from observational studies indicates the benefit of antiviral treatment for hospitalized persons even when treatment is delayed. Antiviral treatment should not be stopped based on negative RIDT results. Infection control measures should be implemented immediately upon admission for any hospitalized patient with suspected influenza even if RIDT results are negative.

Influenza-Associated Pediatric Mortality

- As part of Utah's system to detect influenza-associated pediatric mortality, the Office of the Medical Examiner (OME) tests for influenza virus on all pediatric deaths with compatible symptoms. Therefore, most influenza-associated pediatric mortality cases are identified first through the OME. Whether a case is classified as an influenza-associated pediatric mortality takes into account hospitalization records, medical history, the autopsy report, and the case classification. Because autopsy reports can take several months to complete, the process is not timely and cases are not used to evaluate the influenza season. Pediatric influenza-associated deaths should be managed as follows:
- UDOH epidemiology staff will send a fax to the OME requesting demographic data on the patient and the completed autopsy report.
- Once the residence of the case is known, the local health department will be notified.
- The local health department will usually investigate as much as they can through hospitalization records.
- The OME will send UDOH epidemiology the final autopsy report, which will be forwarded on to the local health department, and public health will decide whether the case can be classified as a pediatric influenza-associated death.

Outbreaks

A state-wide outbreak effectively occurs every year during influenza season when influenza-like illness levels increase above threshold. General measures to control activity during influenza season include vaccination, respiratory etiquette, and staying home when sick.

However, localized outbreaks can occur, and may require additional intervention from public health. Outbreaks of healthcare-associated influenza can occur and affect both patients and personnel in long-term care facilities and hospitals. For more information, see CDC's Influenza Infection Control in Health Care Facilities.

School outbreaks, particularly in daycare and elementary facilities, can occur and can spread very quickly because of close contact and decreased hygiene habits of younger children. In

some situations, schools have had to close because of the high number of absences in students and teachers. Teaching children appropriate hygiene and respiratory etiquette and instituting isolation policies for sick children during influenza season can help control the spread of disease. For more information, see CDC's Seasonal Flu Information for Schools & Childcare Providers.

Case Contacts

Identification

Contacts of influenza cases are usually not traced. Certain situations may warrant contact tracing, such as exposure in a setting with substantial high risk contacts or certain outbreaks. The decision to track case contacts should be made by public health and should follow CDC guidelines.

Management

In the event that case contacts are tracked, management should follow CDC guidelines.

✓REFERENCES

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